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ALDACTONE

The recent introduction of spironolactone (Aldactone - Searle) as a diuretic agent marks an important advance in diuretic therapy. Aldactone does not eliminate the need for other diuretics; but when used along with them it permits the successful management of many patients with edema or ascites who have been refractory to other diuretic measures.

The spirolactones - the family which includes spironolactone - are synthetic steroids in which the side chain of carbon atom-17 is replaced by a lactone ring. By virtue of this modification, Aldactone blocks the action of aldosterone, a compound which may be secreted in excessive amounts in edematous states, and which promotes the retention of sodium and the loss of potassium in the distal renal tubule. Although in most cases aldosterone is only one of several factors involved in sodium retention, the diuretic effectiveness of Aldactone has been clearly established in clinical practice. Unlike other diuretics, Aldactone does not cause potassium loss, and when it is combined with other diuretics, it reduces their kaluretic effect.

EFFECTIVENESS - Aldactone is sometimes effective when used alone, but its chief value is in combination with other diuretics. Ascites of liver cirrhosis resistant to conventional diuretics or to Aldactone alone has been treated successfully with such a combination (S. Shaldon, et al., Lancet, 1:609, 1960; B. F. Clowdus, et al., Proc. Staff Meetings Mayo Clinic, 35:97, 1960). Unpublished studies indicate that the drug is often effective in treating the edema of nephrosis (in this condition aldosterone output is known to be high).

Aldactone is by no means universally successful against edema resistant to other diuretic measures, however. The combination of Aldactone with conventional diuretics has been relatively ineffective thus far in resistant edema of cardiac patients, probably because of the greater depression of glomerular filtration in the latter (no agent acting on the kidney can be expected to compensate for extreme myocardial insufficiency). The drug does not appear to be effective in acute glomerulonephritis or toxemia of pregnancy.

DOSAGE AND TOXICITY - Aldactone is available in 100-mg. tablets. Although the usual recommended daily dose is 400 mg. (administered in divided doses), 600 or 800 mg. may prove necessary in some instances and doses as

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high as 1600 mg. have been used. Aldactone appears to have very low toxicity. Doses of 400 mg. per day have been administered for periods of six months, and much larger doses for shorter periods; no serious toxicity has yet been reported. Mild headaches and mental fuzziness may occur with the smaller doses, drowsiness and mild abdominal pain with the larger ones. There have been occasional rashes which cleared when the drug was stopped. No undesirable renal effects have been reported and there has been no hepatic toxicity.

Because of its high cost (about $1 per 100-mg. tablet, or $4 for a 400-mg. daily dose) the drug will generally be used in combination with the thiazides and parenteral mercurial diuretics only when the edema is refractory to these drugs, as in many cases of liver cirrhosis with ascites. Further experience may indicate other conditions - presumably conditions in which excess aldosterone plays an important role - in which Aldactone is also valuable. In these, it may prove to have diagnostic as well as therapeutic usefulness. Aldactone is unquestionably an important and welcome addition to diuretic therapy.

FIVE VASOPRESSORS

(The March 18th issue of The Medical Letter carried a general review of the use of vasopressors for the treatment of shock; two vasopressors, Levophed and Aramine, were discussed in the April 15th issue. The following discussion of other vasopressor drugs completes the review of this subject.)

I. WYAMINE - Mephentermine (Wyamine - Wyeth) has been used successfully for the shock of myocardial infarction, and is also a satisfactory vasopressor for other types of shock. Wyamine decreases peripheral resistance, yet, because of its effect on heart muscle contractility, it may, like epinephrine, increase cardiac output. Unlike epinephrine, it does not increase ventricular irritability with the consequent risk of arrhythmias. Unlike most other vasopressors, it does not always produce renal vasoconstriction; nor does it decrease cerebral blood flow when given in pressor doses. Its effects are evident one to two minutes after intravenous injection, and five to eight minutes after intramuscular injection, and they last for about 30 to 45 minutes. Wyamine is given intravenously as an infusion (1 mg. per minute in diluent until the desired response is obtained) or in direct injections of 5 to 15 mg.; the intramuscular dose is 20 to 40 mg. Moderate tachyphylaxis may develop with prolonged use but it can usually be overcome by increasing the dosage.

II. METHEDRINE - Methamphetamine (Methedrine - Burroughs, Wellcome; and other brands) is comparable to Wyamine in its cardiovascular effects. It differs, however, in causing relatively pronounced central-nervous-system stimulation; and its cardiovascular effects can be achieved only at the expense of such stimulation.

III. VASOXYL - Methoxamine (Vasoxyl - Burroughs, Wellcome) is especially useful in anesthesiology because of its long duration of action (about an hour), its failure to induce ventricular arrhythmias, and the absence of tachyphylactic effect. It is as powerful a peripheral vasoconstrictor as Levophed but it acts over

a longer period. Vasoxyl acts only peripherally, increasing vascular resistance without increasing cardiac output. Other vasopressors with at least some positive inotropic effect are likely to be preferable for shock associated with myocardial infarction. Vasoxyl is given intravenously as an infusion (20 to 40 mg. in 250 cc.) or in single doses of 2 to 5 mg.; intramuscularly it is given in doses of 10 to 15 mg.

IV. NEO-SYNEPHRINE - Phenylephrine (Neo-Synephrine - Winthrop; and other brands), a peripheral vasoconstrictor with little direct myocardial effect, is comparable to Vasoxyl except that its duration of action is about one-quarter to one-third that of Vasoxyl. Because of its relatively brief action, it is best given intravenously as a slow infusion (20 mg. per liter of diluent). As a single intravenous injection, the dosage is 0.5 to 1 mg.; it is best to start with 0.5 mg.

V. EPINEPHRINE - Epinephrine, when given in slow intravenous infusions, and when sufficiently diluted, increases peripheral blood flow without producing pronounced increases in mean blood pressure (it characteristically increases systolic but lowers diastolic pressure). Marked variability of response from patient to patient, however, and the pronounced and often dangerous increase in ventricular irritability which it causes, generally preclude the use of epinephrine as a vasopressor. It is most useful in those rare situations where a strongly positive inotropic agent is indicated (as during resuscitation following cardiac arrest).

SUMMARY - With the multiplicity of preparations available, it is recommended that the physician use and become thoroughly familiar with one or two. Levophed has had the greatest use in the treatment of medical shock but the need for continuously supervised intravenous administration and the risk of sloughs will make other drugs preferable for many physicians. Despite the inadequacy of clinical experience with many of these drugs, there is enough evidence to indicate that Aramine, Wyamine and Vasoxyl are all satisfactory drugs and any one of them might well be the first choice for most cases of shock.

METRECAL

Metrecal (Mead Johnson) is a powdered food product offered to physicians and consumers as a "medically proven" "new reducing plan." The February issue of Pageant magazine hailed it, less conservatively, as a "new and truly revolutionary concept in weight control," and "a remarkable food concentrate."

COMPOSITION - Metrecal is not the first "formula diet" (see A. R. Feinstein, et al., Ann. Int. Med., 48: 330, 1958), though the precise mixture of food elements is new. It is made from skim milk and whole milk, soya flour, starch, corn and coconut oils, suspending and flavoring agents, vitamins and minerals. A half-pound can makes one quart of low-sodium liquid diet which supplies 900 calories, 70 Gms. of high quality protein, and essential minerals and vitamins.

There is one published study on Metrecal (R. J. Antos, S.W. Med. Mag., 40: 695, 1959), and it is no great surprise that loss of weight was observed in the 75 patients who were able to stay on the recommended diet of one can of Metre-

cal per day for 12 days (100 patients started but 25 dropped out of the trial). The average weight loss for the entire initial group of 100 subjects is reported as 6.5 pounds, or 3.9% of the initial body weight. A considerable portion of this initial loss must be credited to diuresis from reduction of sodium intake.

SIDE EFFECTS - As for side effects, the authors report that "in addition to the major complaints - various types of gaseousness, diarrhea, or constipation - two patients reported nausea and two complained of weakness, one experienced cramps and one urticaria. In all, 28 of the 100 subjects reported a total of 41 undesirable symptoms. Usually these were not serious enough to cause the patient to discontinue the formula."

It seems reasonable to conclude from this study that Metrecal is effective, safe and accepted by many patients for a period of 12 days. But the significance of a 12-day trial in relation to the long-term problem of weight reduction is questionable. Almost any special diet or other reducing measure will work for a while. But, as Dr. A. R. Feinstein points out (J. Chronic Dis., 11: 349, 1960), the problem is not a lack of suitable diets, but the patient's inability to accept long-term modification of dietary habits. It is doubtful that Metrecal solves this problem.

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